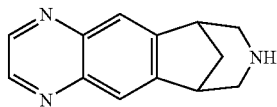


1

**TARTRATE SALTS OF  
5,8,14-TRIAZATETRACYCLO[10.3.1.0<sup>2,11</sup>.0<sup>4,9</sup>]-  
HEXADECA-2(11),3,5,7,9-PENTAENE AND  
PHARMACEUTICAL COMPOSITIONS  
THEREOF**

This application is a continuation of U.S. Ser. No. 10/139,730, filed May 6, 2002 now U.S. Pat. No. 6,890,927, which claims the benefit of U.S. Provisional Application Ser. No. 60/290,861, filed May 14, 2001.

The present invention is directed to the tartrate salts of 5,8,14-triazatetracyclo[10.3.1.0<sup>2,11</sup>.0<sup>4,9</sup>]-hexadeca-2(11),3,5,7,9-pentaene:



and pharmaceutical compositions thereof. The present invention in particular is directed to the L-tartrate salt, and further to the various polymorphs of the L-tartrate salt, including two distinct anhydrous polymorphs (referred to herein as Forms A and B) and a hydrate polymorph (referred to herein as Form C). In addition, the present invention is also directed to the D-tartrate salt of 5,8,14-triazatetracyclo[10.3.1.0<sup>2,11</sup>.0<sup>4,9</sup>]-hexadeca-2(11),3,5,7,9-pentaene and the various polymorphs thereof; as well as the D,L-tartrate salt thereof and its polymorphs, and the meso-tartrate salt thereof and its polymorphs.

The compound, 5,8,14-triazatetracyclo[10.3.1.0<sup>2,11</sup>.0<sup>4,9</sup>]-hexadeca-2(11),3,5,7,9-pentaene, binds to neuronal nicotinic acetylcholine specific receptor sites and is useful in modulating cholinergic function. This compound is useful in the treatment of inflammatory bowel disease (including but not limited to ulcerative colitis, pyoderma gangrenosum and Crohn's disease), irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, amyotrophic lateral sclerosis (ALS), cognitive dysfunction, drug/toxin-induced cognitive impairment (e.g., from alcohol, barbiturates, vitamin deficiencies, recreational drugs, lead, arsenic, mercury), disease-induced cognitive impairment (e.g., arising from Alzheimer's disease (senile dementia), vascular dementia, Parkinson's disease, multiple sclerosis, AIDS, encephalitis, trauma, renal and hepatic encephalopathy, hypothyroidism, Pick's disease, Korsakoff's syndrome and frontal and subcortical dementia), hypertension, bulimia, anorexia, obesity, cardiac arrhythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supramuscular palsy, chemical dependencies and addictions (e.g., dependencies on, or addictions to nicotine (and/or tobacco products), alcohol, benzodiazepines, barbiturates, opioids or cocaine), headache, migraine, stroke, traumatic brain injury (TBI), obsessive-compulsive disorder (OCD), psychosis, Huntington's chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct dementia, age-related cognitive decline, epilepsy, including petit mal absence epilepsy, attention deficit hyperactivity disorder (ADHD), Tourette's Syndrome, particularly, nicotine dependency, addiction and withdrawal; including use in smoking cessation therapy.

The tartrate salts of this invention may also be used in a pharmaceutical composition in combination with an antidepressant such as, for example, a tricyclic antidepressant or a

2

serotonin reuptake inhibiting antidepressant (SRI), in order to treat both the cognitive decline and depression associated with AD, PD, stroke, Huntington's chorea or traumatic brain injury (TBI); in combination with muscarinic agonists in order to stimulate both central muscarinic and nicotinic receptors for the treatment, for example, of ALS, cognitive dysfunction, age-related cognitive decline, AD, PD, stroke, Huntington's chorea and TBI; in combination with neurotrophic factors such as NGF in order to maximize cholinergic enhancement for the treatment, for example, of ALS, cognitive dysfunction, age-related cognitive decline, AD, PD stroke, Huntington's chorea and TBI; or in combination with agents that slow or arrest AD such as cognition enhancers, amyloid aggregation inhibitors, secretase inhibitors, tau kinase inhibitors, neuronal anti-inflammatory agents and estrogen-like therapy.

Compounds that bind to neuronal nicotinic receptor sites, including 5,8,14-triazatetracyclo[10.3.1.0<sup>2,11</sup>.0<sup>4,9</sup>]-hexadeca-2(11),3,5,7,9-pentaene, and its hydrochloride salt, are referred to in WO 99135131, published Jul. 15, 1999 (corresponding to U.S. Ser. No. 09/402,010, filed Sep. 28, 1999 and U.S. Pat. No. 09/514,002, filed Feb. 25, 2000). The foregoing applications, owned in common with the present application and incorporated herein by reference in their entirety, generically recite pharmaceutically acceptable add addition salts for the compounds referred to therein.

The L-tartrate salt of the present invention exhibits properties, including those of high solid-state stability and compatibility with certain drug product formulation excipients, that render it superior to previously known salts of 5,8,14-triazatetracyclo[10.3.1.0<sup>2,11</sup>.0<sup>4,9</sup>]-hexadeca-2(11),3,5,7,9-pentaene. Further, the D-tartrate and D,L-tartrate salts exhibit properties that also make them appropriate for drug product formulation use.

#### BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a powder X-ray diffraction of the anhydrous L-tartrate salt Form A of 5,8,14-triazatetracyclo[10.3.1.0<sup>2,11</sup>.0<sup>4,9</sup>]-hexadeca-2(11),3,5,7,9-pentaene (y axis is linear counts per second; X in degrees 2 theta).

FIG. 2 is the powder X-ray diffraction of the anhydrous L-tartrate salt Form B of 5,8,14-triazatetracyclo[10.3.1.0<sup>2,11</sup>.0<sup>4,9</sup>]-hexadeca-2(11),3,5,7,9-pentaene (y axis is linear counts per second; X in degrees 2 theta).

FIG. 3 is the powder X-ray diffraction of the L-tartrate salt hydrate Form C of 5,8,14-triazatetracyclo[10.3.1.0<sup>2,11</sup>.0<sup>4,9</sup>]-hexadeca-2(11),3,5,7,9-pentaene (y axis is linear counts per second; X in degrees 2 theta).

FIG. 4A is the calculated powder X-ray diffraction pattern of the anhydrous Form B L-tartrate salt of 5,8,14-triazatetracyclo[10.3.1.0<sup>2,11</sup>.0<sup>4,9</sup>]-hexadeca-2(11),3,5,7,9-pentaene (y axis is linear counts per second; X in degrees 2 theta). FIG. 4B is the calculated powder X-ray diffraction pattern of the Form C L-tartrate salt hydrate of 5,8,14-triazatetracyclo[10.3.1.0<sup>2,11</sup>.0<sup>4,9</sup>]-hexadeca-2(11),3,5,7,9-pentaene (y axis is linear counts per second; X in degrees 2 theta).

FIG. 5A is the calculated powder X-ray diffraction pattern (lower trace) laid over the observed X-ray diffraction pattern (upper trace) for the anhydrous Form B L-tartrate salt of 5,8,14-triazatetracyclo[10.3.1.0<sup>2,11</sup>.0<sup>4,9</sup>]-hexadeca-2(11),3,5,7,9-pentaene (y axis is linear counts per second; X in degrees 2 theta). FIG. 5B is the calculated powder X-ray diffraction pattern (lower trace) laid over the observed X-ray diffraction pattern (upper trace) for the Form C L-tartrate salt hydrate of 5,8,14-triazatetracyclo[10.3.1.0<sup>2,11</sup>.0<sup>4,9</sup>]-hexa-